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EVOLUTION OF PATIENTS WITH AIDS AFTER cART: CLINICAL AND LABORATORY EVOLUTION OF PATIENTS WITH AIDS AFTER 48 WEEKS OF ANTIRETROVIRAL TREATMENT

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SUMMARY

Combination Antiretroviral Therapy (cART) aims to inhibit viral replication, delay immunodeficiency progression and improve survival in AIDS patients. The objective of this study was to compare two different schemes of cART, based on plasma viral load (VL) and CD4+ T lymphocyte count, during 48 weeks of treatment. For this purpose, 472 medical charts of a Specialized Outpatient Service were reviewed from 1998 to 2005. Out of these, 58 AIDS patients who had received a triple drug scheme as the initial treatment were included in the study and two groups were formed: Group 1 (G1): 47 individuals treated with two nucleoside reverse-transcriptase inhibitors (NRTI) and one non-nucleoside reverse-transcriptase inhibitor; Group 2 (G2): 11 patients treated with two NRTI and one protease inhibitor. In G1 and G2, 53.2% and 81.8% respectively were patients with an AIDS-defining disease. The T CD4+ lymphocyte count increased progressively up until the 24th week of treatment in all patients, while VL became undetectable in 68.1% of G1 and in 63.6% of G2. The study concluded that the evolutions of laboratory tests were similar in the two treatment groups and that both presented a favorable clinical evolution.

KEYWORDS: HIV/AIDS; Antiretroviral Therapy; CD4+ T Lymphocyte Count; Viral Load of HIV.

INTRODUCTION

AIDS is characterized by severe immunosuppression associated with the appearance of opportunistic infections and certain types of neoplasias[1]. There were 608,230 cases officially reported in Brazil from 1980 to June 2011, 56% of which were identified in the southeastern region of the country[20].

Combination Antiretroviral Therapy (cART) aims to inhibit viral replication, delay the progression of immunodeficiency and thereby restore immunity, albeit partially, in order to combat or prevent the emergence of opportunistic infections, thus increasing patient survival and improving quality of life. This tendency is observed throughout the world by declines in morbidity and mortality among AIDS patients[26,27].

The risk of progression of HIV infection to the development of AIDS or to death is initially related to an elevated HIV viral load (VL), and subsequently to a low count of CD4+ T lymphocytes[3,4]. These markers are considered the principal to evaluate the clinical status of the patient and to monitor and indicate the start of cART[19], following recommendations specific to each country, which have been changed over time[21,22].

Currently, the initial therapy must include at least three drugs: two nucleoside reverse-transcriptase inhibitors (NRTI) associated with one non-nucleoside reverse-transcriptase inhibitor (NNRTI) or with one protease inhibitor (PI), preferentially with administration of ritonavir for pharmacokinetic enhancement**.** Schemes with NNRTI are suggested as the first option for patients naïve to treatment who start cART[21].

Not all patients under cART exhibit a rise in CD4+ T cell counts despite viral suppression[11,12,38,39]. This observation has been assigned to factors related to pre-therapy CD4+ T counts and VL, age at treatment initiation and time to reach viral suppression after the start of therapy. It is possible that cumulative VL during cART may also influence the recovering of CD4+ T counts and the risk of AIDS-defining events, suggesting that therapeutic schemes which result in a faster reduction and sustained suppression of the viral load could also lead to a more favorable clinical evolution and immune response[17].

The occurrence of treatment failure must be promptly diagnosed. Failure to respond to a therapeutic scheme may occur for different reasons including inadequate compliance, presence of co-morbidities, previous viral resistance to one or more therapeutic agents, altered gastrointestinal absorption, drug interactions and low potency of the ARV scheme[21].

The objective of this study was to compare two different cART schemes in patients previously naïve to treatment, according to the

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achievement of undetectable VL and the increase in CD4+T lymphocyte count, during 48 weeks of treatment.

MATERIAL AND METHODS

In the period from January 1998 to December 2005, 472 medical charts from the Specialized Outpatient Service and Day Hospital "Domingos Alves Meira" from Botucatu Medical School, Univ. Estadual Paulista (UNESP), were selected for the study. Of these, 147 were excluded since they were inactive in the Medical File.

The inclusion criteria were patients of both sexes with confirmed HIV infection, at least 18 years of age, naïve to cART and who had been monitored for at least 48 weeks, with T CD4+ count and VL determinations each repeated four times during the period. According to these inclusion criteria and because many patients had lost follow up, only 58 of the 325 individuals were enrolled in the study. This number represented about 15% of the overall patients of the Service.

Data collection was accomplished by retrospective analysis of the patients medical charts using a previously elaborated and tested formula, considering the following aspects: age, sex, origin, risk factors for HIV infection, classification of HIV infection according to the CDC (Centers for Disease Control and Prevention)[4] system, clinical manifestations (diseases associated with AIDS, regardless of CD4+ T cell count), CD4+T cell count, HIV VL determination and the cART scheme. The frequency of analysis of clinical and laboratory parameters considered in the study were at 04, 12, 24 and 48 weeks after the cART initiation.

The counts of CD4+ T lymphocytes and establishment of CV i.e. plasma quantification of HIV-1 RNA were accomplished by the flow cytometry technique and by the *branched*-DNA method respectively, during the routine medical visits of patients at the Botucatu Hemocenter, UNESP. The results were expressed as absolute numbers per cubic millimeter of blood (cells/mm^3) and as absolute numbers of virus copies RNA per milliliter of plasma and base-10 logarithm (log 10).

The patients were divided into two study groups. Group 1 (G1): 47 individuals in treatment with two NRTIs and one NNRTI. Group 2 (G2): 11 patients under treatment with two NRTIs and one PI.

Statistical analysis: Descriptive surveying of sociodemographic characteristics, comparison between schemes in relation to the numeric variables by means of the Mann-Whitney Test, Fisher's Exact Test and Chi-Square, at a significance level of $\alpha = 0.05$, to study the association between the schemes and the categorical variables. The comparison between the moments of laboratory evaluation in each scheme was accomplished by the Friedman test, at $\alpha = 0.05$ significance level. There were no missing variables at each key time point.

This project was analyzed and approved by the Research Ethics Committee of the Botucatu Medical School, UNESP.

RESULTS

Fifty-eight patients were studied, 34 (58.6%) were male and 24 (41.4%) female; the median age was 32.5 years, with a range from 21 to 65 years.

Table 1 shows the distribution of the subjects of the study based on mean age, sex, risk factors for HIV infection, classification of HIV infection according to CDC, presence or absence of co-morbidities and clinical manifestations prior to cART. There was no statistical difference between the two groups in relation to these variables.

Twenty-four (41.4%) patients were not presenting an AIDS-defining disease during the study development, while the majority of them, 34 (58.6%), had manifestations of mild or severe immunodeficiency, including persistent generalized lymphadenopathy, oral and esophageal candidiasis, pneumocystosis, toxoplasmosis, tuberculosis, cytomegalovirus, herpes zoster, cryptosporidiosis, neurological manifestations of Chagas' disease, recurrent pneumonia, molluscum contagious, strongyloidiasis and onychomycosis.

Thirty-six patients (62.1%) showed one or more of the following behavior or co-morbidities at the moment of cART initiation: substance abuse, tobacco smoking, alcoholism, hepatitis virus B or C, condyloma acuminata, syphilis, peptic ulcer, psoriasis, *tinea corporis*, depression, diabetes *mellitus*, obesity, dyslipidemia, systemic arterial hypertension, osteoporosis, hemorrhagic stroke, panic disorder and mental deficiency.

Table 2 shows the patients' evolution after 48 weeks of treatment, at which point no statistically significant differences were found between the two study groups. Clinical improvement of immunodeficiency manifestations and laboratory parameters was shown in 13 cases (22.4%). However, in five (8.7%) patients, all of them of G1, the clinical manifestations had worsened.

The evolution of CD4+T counts is described in Figure 1, including medians of the laboratory results during 48 weeks of monitoring. There was no significant difference between the groups in the evaluations at each time studied, nor when the 24th and 48th weeks were compared. Despite the fact that the CD4+T counts at the 4th, 12th, 24th and 48th weeks were significantly higher than at the pre-treatment phase in G1, this was not observed in G2. Furthermore, there was a median gain of 155 cells/mm^3 in all patients; 169 cells/mm^3 in G1 and 144 cells/mm^3 in G2.

With regard to the CD8+T lymphocyte counts, there was no difference between the groups at any time or between the times studied in each scheme. The medians in G1 and G2 were 723 cells/mm^3 (478-1162) and 686 cells/mm^3 (354-952) respectively in the pre-treatment phase, and 789 cells/mm^3 (539-1113) and 848 cells/mm^3 (480-1452) at the end of analysis (data not shown in Tables or Figures).

Figures 2 and 3 reveal the distribution of patients in the two groups throughout the 48 weeks according to the CD4+ T lymphocytes count. At the end of the 48 weeks, most of the patients of both groups were in the range between 200 and 400 cells/mm^3, although there was no statistically significant difference between the two groups.

The analysis of plasma VL determinations is also shown in these Figures. In the first determination after four weeks of treatment, 19 (36.2%) patients of G1 and two (18.2%) of G2 achieved undetectable VL. At the end of the 48-week observation period, 32 (68.1%) patients of G1 and seven (63.6%) of G2 presented undetectable VL. No statistically significant difference was found between the two groups.

Table 1
Characterization of 58 patients infected by HIV prior the first scheme of potent antiretroviral treatment

Characteristics	G1		G2		Total	
Age (median)	32.0 (IQ 1-3: 28.5 - 39)		40.0 (IQ 1-3: 27 - 44.5)		32.5 (IQ 1-3: 28 - 40)	
Sex	N	(%)	N	(%)	N	(%)
Male	27	57.4	07	63.7	34	58.6
Female	20	42.6	04	36.4	24	41.4
Risk factors for HIV						
Heterosexuals	30	63.8	08	72.7	38	65.5
Male Homo/Bisexuals	09	19.1	01	9.1	10	17.2
IV* drug users	04	8.5	02	18.2	06	10.3
Homo/Bi. + IV* drug users	02	4.3	00	00	02	3.4
Blood transfusion	01	2.1	00	00	01	1.7
Occupational accident	01	2.1	00	00	01	1.7
CDC classification						
Stage B1	00	00	01	9.1	01	1.7
Stage B2	05	10.3	00	00	05	8.6
Stage B3	23	48.9	03	27.7	26	44.8
Stage C2	05	10.3	02	18.2	07	12.1
Stage C3	14	29.8	05	45.5	19	31.0
Co-morbidities**						
Presence	32	68.1	04	36.4	36	62.1
Absence	15	31.9	07	63.6	22	37.9
Manifestation of AIDS***						
Presence	25	53.2	09	81.8	34	58.6
Absence	22	46.8	02	18.2	24	41.4

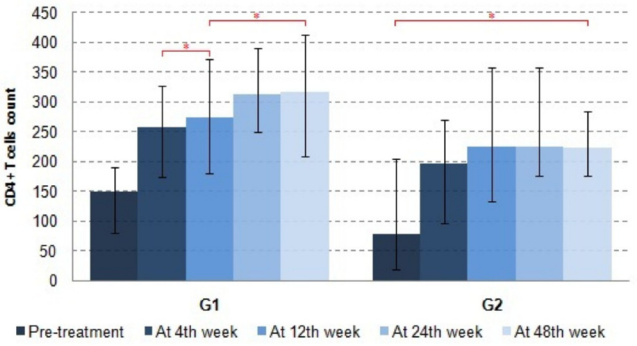
*IV: Intravenous; **Hepatitis virus B or C, condyloma acuminata, syphilis, peptic ulcer, psoriasis, *tinea corporis*, depression, diabetes *mellitus*, obesity, dyslipidemia, systemic arterial hypertension, osteoporosis, hemorrhagic stroke, panic disorder and mental deficiency; ***Generalized lymphadenopathy, oral and esophageal candidiasis, pneumocystosis, toxoplasmosis, tuberculosis, cytomegalovirus, herpes zoster, cryptosporidiosis, neurochagas, recurrent pneumonia, molluscum contagious, strongyloidiasis and onychomycosis. G1: 2 nucleoside reverse transcriptase inhibitors + 1 non-nucleoside reverse transcriptase inhibitor; G2: 2 nucleoside reverse transcriptase inhibitors + 1 protease inhibitor. Chi-Square: $p > 0.05$ (G1 = G2).

Table 2
Clinical evolution of 58 patients after 48 weeks of antiretroviral treatment

Evolution	G1		G2		TOTAL	
	N	(%)	N	(%)	N	(%)
Absence of C.M.*	04	8.5	02	18.1	06	10.3
Unaltered clinical chart (C.M.)	25	53.2	03	27.3	28	48.2
Clinical improvement	10	21.3	03	27.3	13	22.4
Clinical worsening	05	10.6	00	00	05	8.7
Death	01	2.2	00	00	01	1.7
Abandonment of treatment	02	4.2	03	27.3	05	8.7

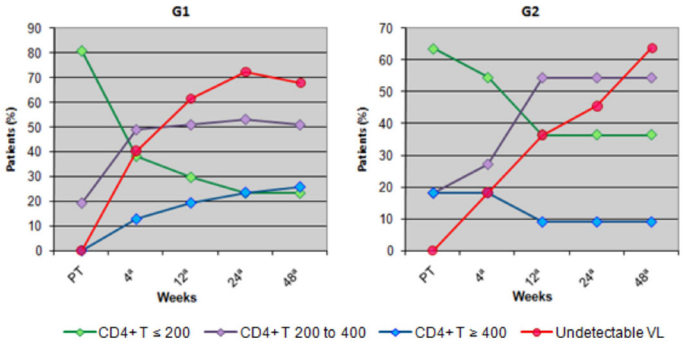
*C.M. - Clinical manifestation. G1: 2 nucleoside reverse transcriptase inhibitors + 1 non-nucleoside reverse transcriptase inhibitor; G2: 2 nucleoside reverse transcriptase inhibitors + 1 protease inhibitor. Chi-Square: $p > 0.05$ (G1 = G2).

The median, first, and third quartile of VL quantification in the pre-treatment phase was 68000 (14350-102641) viral copies/mm^3 in G1 and 6300 (945-134500) in G2. Only in G1 was there a difference between the VL at this time and at the 4th (G1: 395 [133-1239] and G2: 1900 [412-38656]) and 12th weeks (G1: 488 [112-3057] and G2: 730 [171-32591]) after starting cART. No difference was found between VL values of the pre-treatment phase and after 48 weeks of treatment in both groups (G1: 8668 [1594-73675]; G2: 14976 [2762-243176]). Nevertheless, patients



G1: 2 nucleoside reverse transcriptase inhibitors + 1 non-nucleoside reverse transcriptase inhibitor; G2: 2 nucleoside reverse transcriptase inhibitors + 1 protease inhibitor. Friedmann: $p < 0.05$ (comparison between moments in G1); $p > 0.05$ (comparison between moments in G2). Mann-Whitney: $p > 0.05$ (G1 = G2). * Groups do not differ statistically, when comparing the different moments in each scheme.

Fig. 1 - Median, 1st and 3rd quartile refer to T CD4+ lymphocytes count by scheme and treatment moment.



G1: 2 nucleoside reverse transcriptase inhibitors + 1 non-nucleoside reverse transcriptase inhibitor; G2: 2 nucleoside reverse transcriptase inhibitors + 1 protease inhibitor. PT in the x-axis: pre-treatment. Chi-Square: $p > 0.05$ (G1 = G2). Chi-Square: $p > 0.05$ (G1 = G2). p value between "viral load undetectable" from groups 1 and 2: before treatment, $p = 0$; 4th week, $p = 0.167$; 12th week, $p = 0.127$; 24th week, $p = 0.087$; 48th week, $p = 0.777$.

Fig. 2 and 3 - Distribution of patients from groups 01 (G1) and 02 (G2), according to T CD4+ lymphocytes count and the percentage evolution of groups with undetectable viral load across 48 weeks of treatment.

of G1 who had presented higher levels of viral load at the start of therapy showed a greater decrease in these levels after 48 weeks (data not shown in Tables or Figures).

DISCUSSION

In the present study, the majority of the patients were between the ages of 25 and 49. This is in accordance with previous data reported in Brazil, although cases in individuals above 50 years old is increasing[20]. Males were predominant in the study, consistent with the tendency observed in the national context, although the growing number of women infected by the virus must be considered[2,20].

As for the mechanisms of HIV transmission, most of the patients in this study were classified in the heterosexual risk category, regardless of gender. In the state of São Paulo, and in Brazil as a whole, individuals in this risk category have been predominating in recent years, mainly among women[2,20].

High potency AIDS therapy schemes are responsible for altering the progression of the disease – decreasing both the incidence of opportunistic infections and the proportion of deaths – since they produce durable immunological responses characterized by a reduction in HIV plasma VL levels and an increase in CD4+ T lymphocyte counts in the majority of patients[24,34,35,37]. SCHOOLEY[34] described the impact of these treatments on AIDS mortality in a review, and exemplified this reality with the study of PALELLA *et al.*[27], carried out with 1255 patients from nine cities in the United States of America. These authors found a decrease from 29.4% to 8.8% in the proportion of fatalities among the group of patients with CD4+ T counts below 100 cells/mm^3 one year after the approval of this new therapy.

However, the best initial regimen is also related to better prognosis. According to LI *et al.*[16] in 2011, immunological and virological responses in the first five years after cART initiation strongly influenced these same responses in the subsequent 5-7 years. Also, patients who responded well to the first or second cART regimens maintained higher CD4+ counts and lower HIV RNA than those who switched regimens at least twice. In a multicohort study[30] in Africa and Asia with 632 patients on second-line cARV for more than six months, it was reported that almost 20% of them displayed WHO clinical, immunological or virological criteria of failure after a median of 12 months of follow up, with cumulative probabilities showing up to 28% of failures at two years. In contrast to the study above, our results showed some clinical worsening or death in 10.4% of patients after 48 months.

Furthermore, we observed in the present study that schemes containing NNRTI were more frequently used (81%) than those with PI (18.9%). These data are similar to those found in a study by SANTOS *et al.*[33] in 2009 in the state of Goiás, Brazil, that included 222 patients, 160 (72%) of whom were using NNRTI, emphasizing the combination of zidovudine (AZT), lamivudine (3TC) and efavirenz (EFV). In the same country, the findings of CUÉLLAR[7] between the years 2002 and 2003 in Recife in the state of Pernambuco, obtained from monitoring 69 patients for 12 months, also demonstrated that the use of NNRTI was more common in 72.5% of cases and the combination AZT+3TC+EFV was the most indicated. In this same study, the authors found nelfinavir among the most used PI also with the association AZT and 3TC[7]. All these data are consistent with studies of about 5,000 patients conducted in Latin America and the Caribbean, with the indication of NNRTI as part of the initial regimen in 84% of them, while EFV was the most frequently used drug (58.5%)[5]. However, in the present study the schemes were not differentiated by drug, but rather by drug class only.

The present study has found an increase in CD4+ T lymphocytes counts in both groups. After 12 weeks of treatment, G1 and G2 presented an equal mean increase of 141 cells and 144 cells. FERRADINI *et al.*[8] in Cambodia, Asia, showed that a strong immune reconstitution was observed after 24 months (gain of 258 cells/mm^3 [IQR: 136- 425]) of follow-up on second-line cART regimens. In 2010 in Brazil, a study by SANTOS *et al.*[33] that compared these cell counts before and after 36 months of treatment regardless of the ARV scheme used, demonstrated an average increase of 225 T CD4+ cells. The less expressive increase in the T CD4+ counts found in our study was probably due to the short follow- up period of only a few months. Additionally, the lower CD4+ T cells count at cART initiation, which strongly predicts progression in the first five years after cART[6], could have led to a slower immune restoration, together with the high VL values observed in the pre-treatment phase.

SOUZA *et al.*[37] , in a study between 1996 and 2001 in Botucatu City, São Paulo State, Brazil, found a mean increase of $CD4^+$ T cell counts in patients treated with a combination of NNRTI that did not differ statistically from those of patients treated with PI. In the present study, a statistical difference was found only in G1 when comparing pre-treatment $CD4^+$ T lymphocyte counts with those after 4, 12, 24 and 48 weeks of treatment.

A study from 2004 by ROMANINI *et al.*[32] in Porto Alegre (RS), Brazil, with patients treated with NNRTI (AZT + 3TC + EFV) and PI (AZT + 3TC + atazanavir) found a significant increase in the $CD4^+$ T cell counts in both groups, but no difference when one group was compared to the other. In this study, the increase in the number of $CD4^+$ T lymphocytes was similar to that found in our study, i.e. a median gain of 144 cells in the group treated with PI and 169 cells in the NNRTI-treated group.

Some authors[01,13,27,32,40] have reported better results with triple drug schemes containing NNRTI and PI than double AIDS drug schemes. Nevertheless, internal comparisons do not indicate any difference in the evolution of patients, as observed in the present study wherein both schemes were effective in increasing $CD4^+$ T lymphocyte counts, which was demonstrated by a percentage increase in the portion of patients with more than 200 cells/mm^3 throughout the observation period. The CD4+ T count was below 200/mm^3 before cART in 80.8% of the patients treated with NNRTI and 63.6% of those treated with PI. After 48 weeks of cART these counts were above 200 cells in 76.6% of the NNRTI group and 63.6% of the PI group.

With reference to plasma VL after 36 months of cART, SANTOS *et al.*[33] found that approximately 80% had results below the limit of detection, a proportion higher than that of our study, in which 67.2% of the patients achieved undetectable levels after six months of therapy and maintained this result until the end of the 48 weeks. However, these are better data than those of PINTO NETO *et al.*[29] in 1998 and 1999 in Vitoria (ES), and CASEIRO *et al.*[3] between 1997 and 2003 in Santos (SP) who found 50.0% and 44.0% respectively. The percentages found in the present study are also higher than those registered in the systematic review of BARTLETT *et al.*[1] in the United States of America in 2001, in which the schemes containing PI produced an undetectable viral load in 46.0% of cases versus 51% under NNRTI. Still, other authors[16] showed that participants using triple NRTI-cART were significantly less likely to suppress RNA than those using PI-cART or NNRTI-cART, in a study that involved individuals who were either ART naïve or not at the time of cART initiation.

Nevertheless, it should be emphasized that differences in the methodology adopted by various authors hinders comparison, mainly on account of the inclusion of patients having already experimented with ARV or the maintenance in the study of patients with many changes in therapeutic schemes, since the present study included only patients in their first cART scheme.

The maintenance of undetectable VL was discussed by CASEIRO *et al.*[3]. These authors accompanied patients naïve to cART for six years, and found that only 27.5% remained with levels below the limit of detection after one year of treatment with triple drug schemes, composed of both NNRTI and PI. For SILVEIRA *et al.*[36] and CUÉLLAR[07], an undetectable level as well as its maintenance for the longest possible period of time is associated with factors of compliance or non-compliance to treatment[7,36] such as education level, socioeconomic factors, side effects, the number of doses of medicaments and the evolution of clinical parameters[07]. Some authors[10,16] hypothesized that patient age, HIV-1 disease stage before cART initiation, immunological and virological responses to cART in the first five years of treatment and types of cART regimens would significantly affect later CD4+ count and RNA levels among long-term cART users. However, other factors which occur in the early or late stages of infection can contribute to the defective responses on these parameters, such as low T CD4+ nadir[23] and residual viremia results from cellular reservoirs despite viral suppression[18].

The best time to initiate the treatment and the best choice for a first scheme remain frequent topics of discussion in the literature. Some studies affirm the prudence of postponing the start of therapy on account of its side effects and also because the benefits of the treatment do not outweigh the risks of these effects[31]. According to many authors such as FRENCH *et al.*[9], NIXON & LANDAYB[25] and KAMAT *et al.*[15], persistent chronic inflammation and immune activation are factors potentially determinant of morbidity and mortality not associated with AIDS, even during effective cART. Thus, it is necessary for these parameters to be minimized in order to increase patient survival. Meanwhile, other studies[21,23] have already indicated its earlier use, since the nadir of CD4+ T is considered an important factor for predicting the immune response whereas the ARV combinations independently of the initial scheme showed similar effects on this recuperation[23]. In addition to preventing immune deterioration[23], the early initiation of cART is associated with improved control of diseases both related and unrelated to AIDS[28].

It must also be considered that there is a strong correlation between VL levels of the infected partner at the moment of transmission and the VL values in the acute phase of those recently infected[14], which intensifies the theory of early initiation of ARVs in order to maintain low VL in chronic carriers.

In fact, due to the unavailability of a new review of medical records and the impossibility of performing adjusted analysis, it must be taken into account that the small sample size of this study, the retrospective design and some baseline differences could result in biased interpretation. Hence, larger prospective and long-term evolution studies are needed in order to better evaluate the response and durability of each therapeutic scheme.

CONCLUSION

The present study has shown a favorable evolution of the therapeutic response in up to 48 weeks to the first scheme proposed for individuals naïve to cART, but without difference between the use of NNRTI versus PI.

RESUMO

Evolução de pacientes com AIDS pós cART: evolução clínica e laboratorial de pacientes com AIDS após 48 semanas de tratamento antirretroviral

A terapia antirretroviral na aids visa inibir a replicação viral, retardar a progressão da imunodeficiência e melhorar a sobrevida do paciente. O objetivo do estudo foi comparar dois esquemas de tratamentos antirretrovirais, quanto à carga viral plasmática (CV) e contagem de

linfócitos T CD4+, durante 48 semanas de tratamento, pela revisão de 472 prontuários no período de 1998 a 2005, em um Serviço de Ambulatórios Especializados. Foram incluídos para o estudo 58 pacientes que receberam esquema tríplice como terapêutica inicial, os quais formaram dois grupos: Grupo 1 (G1): 47 indivíduos em tratamento com dois inibidores de transcriptase reversa análogos de nucleosídeos (ITRN) e um inibidor de transcriptase reversa não análogo de nucleosídeo; Grupo 2 (G2): 11 pacientes em tratamento com dois ITRN e um inibidor de protease. Entre os pacientes de G1 e G2, 53.2% e 81.8%, respectivamente, foram classificados como portadores de aids com doença definidora. A contagem de linfócitos T CD4+ aumentou progressivamente até a 24ª semana de tratamento, em todos os doentes e, a CV tornou-se indetectável em 68,1% dos casos de G1 e em 63,6%, do G2. O estudo concluiu que, em ambos os grupos de tratamento, houve evolução laboratorial semelhante e essa observação foi compatível com evolução clínica favorável dos pacientes estudados.

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